REMARKS

Applicants respectfully submit that the pending claims in this application are claims 1 and 34-54, as filed on July 11, 2003 in the Preliminary Amendment.

Applicants provide herewith the support for claim 54, which had been inadvertently omitted from the July 11, 2003 Preliminary Amendment. Support for claim 54 can be found, *e.g.*, in original claims 23 and 24 and on page 11, lines 16-17 of the specification. Applicants had given explicit authorization to the Director in the July 11, 2003 Transmittal Letter for Rule 53(b) Continuing Patent Application, which included the July 11, 2003 Preliminary Amendment, to charge payment of any additional filing fees required under 37 C.F.R. § 1.16 in connection with the filing to Deposit Account No. 06-1075. According to the Official Filing Receipt dated January 23, 2004, it appears that the United States Patent and Trademark Office considered all of claims 1 and 34-54 when they calculated that there was a total of 22 claims. However, in order to ensure that the correct number of claims have been accounted and paid for, applicants hereby authorize the Director to charge payment of any additional claims fee required under 37 C.F.R. § 1.16 to Deposit Account No. 06-1075 in connection with this response.

The Examiner stated in his April 14, 2005 Office Action that "Applicant did not indicate the new and

cancelled limitations" of amended claim 1 in Applicants' July 11, 2003 Preliminary Amendment. Applicants' July 11, 2003 Preliminary Amendment presented amended claim 1 in clean form and also in marked-up form on a separate sheet, in full compliance with the practice required by the United States Patent and Trademark Office at that time (before July 30, 2003 when the current rules took effect). Accordingly, because the Preliminary Amendment filed July 11, 2003, complied with the Rules in effect at the time of submission, applicants respectfully request that the Examiner reconsider his statement with respect to amended claim 1.

Consistent with the election made below, applicants have withdrawn claims 40 and 50-51. None of the amendments adds new matter. Applicants request reconsideration in view of the amendment above and remarks below.

INVENTION RESTRICTION REQUIREMENT

The Examiner has required restriction of the claims of this application under 35 U.S.C. § 121 into one of the following two Groups:

Group I: Claims 1, 34-49 and 52-53*, drawn to compositions comprising a viral vector encoding a

* Applicants believe that claim 54 should also be included as an invention of Group I.

therapeutic gene product and a carrier and methods for increasing the level of a therapeutic gene product and modulating the toxicity associated with a virally-encoded transgene comprising administration of an agent that modulates Kupffer cell function or levels and a viral vector encoding the therapeutic gene product; and

Group II: Claims 50-51, drawn to methods for delivering a virally-encoded transgene in a subject comprising identifying a dosage inflection point of the virus encoding the transgene and comparing the inflection point to the levels of gene product produced in the subject, and adjusting the dosages, if necessary.

The Examiner asserts that the inventions listed as Groups I and II are patentably distinct because they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The Examiner states that Group I requires the administration of an agent that modulates Kupffer cell level or function, while Group II requires the determination of the levels of transgene expression as a function of administered levels of virus. The Examiner states that because these distinct, non-coextensive steps would require different, distinct and non-coextensive considerations which would pose a serious

burden if these two Groups were to be searched and examined together, restriction for examination is required.

First, as discussed above, the pending claims in this application are claims 1 and 34-54, as submitted in the Preliminary Amendment filed July 11, 2003.

Second, applicants elect the subject matter of Group I, with traverse, for further prosecution in this application. Claims 1, 34-49 and 52-54 correspond to the subject matter of Group I (*i.e.*, they are drawn to compositions comprising a viral vector encoding a therapeutic gene product and a carrier and methods for increasing the level of a therapeutic gene product and modulating the toxicity associated with a virally-encoded transgene comprising administration of an agent that modulates Kupffer cell function or levels and a viral vector encoding the therapeutic gene product). This election is made expressly without waiver of applicants' rights to continue to prosecute and to obtain claims to the non-elected and/or canceled subject matter either in this application or in other applications claiming priority herefrom or from a related application. In view of this election, claims 50 and 51 are withdrawn.

SPECIES ELECTION REQUIREMENT

The Examiner states that the claims are directed to more than one species of the generic invention and that

the claims are directed to the following patentably distinct species:

(1) Applicants are required to choose one of the twelve routes of administration from claims 43, 44 and 45; and

(2) Applicants are required to choose a subject that is either rodent or human from claims 40 and 42.

The Examiner has required that applicants elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The Examiner states that claims 1 and 34-38 are generic. The Examiner further states that the reply to the species election must include a listing of all claims readable thereon. The Examiner states that upon allowance of a generic claim, applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of the allowed generic claim. Applicants traverse.

First, applicants traverse the election requirements on the different routes of administration for the viral vector from claims 43 and 44 and for the agent from claim 45 on the basis of the procedures set forth in the Manual of Patent Examining Procedure ("MPEP"). The MPEP states that "election of species should not be required if the species claimed are considered clearly unpatentable (obvious) over each other." MPEP § 808.01(a).

The MPEP further states that there must be unduly extensive and burdensome search required for an election of species to be made. MPEP § 808.01(a).

Applicants respectfully submit that each of the routes of administration recited in claims 43-45 are not in themselves inventive because each of the recited routes of administration was well-known to those of ordinary skill in the art at the priority filing date of the instant application. Because the routes of administration as recited in claims 43-45 are unpatentable over each other in and of themselves, applicants respectfully submit that the MPEP directs that there is no additional burden for the Examiner to search all these routes of administration together. Accordingly, applicants request that the species election with respect to the twelve routes of administration be withdrawn. Purely in the interest of being fully responsive to the Examiner's election of species requirement, applicants elect the species of intravenous administration, with traverse. Claims 1, 34-49 and 54 read on this elected species. This election is made expressly without waiver of applicants' rights to continue to prosecute and to obtain claims to the non-elected and/or canceled subject matter either in this application or in other applications claiming priority herefrom.

Second, applicants traverse the election requirement to choose a subject that is a rodent (claim 40) or human (claim 42). However, in order to expedite

prosecution, applicants elect the species of human, with traverse. Claims 1, 34-42 and 46-49 read on this elected species. This election is made expressly without waiver of applicants' rights to continue to prosecute and to obtain claims to the non-elected and/or canceled subject matter either in this application or in other applications claiming priority herefrom.

CONCLUSION

In view of the above, applicants request that the Examiner examine the pending claims in this application. Applicants request favorable consideration and early allowance of the pending claims.

Respectfully submitted,

James F. Haley, Jr. (Reg. No.27,794)
Stanley D. Liang (Reg. No.43,753)
Attorneys for Applicants
Connie Wong (Limited Recognition)
Agent for Applicants

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1104
Tel.: (212) 596-9000
Fax: (212) 596-9090

Appendix A

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MAY 16 2005
PATENT & TRADEMARK OFFICE

A123 CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Not Yet Assigned
Group Art Unit	:	Not Yet Assigned
Applicants	:	Barsoum, et al.
Application No.	:	Not Yet Assigned
Confirmation No.	:	Not yet assigned
Filed	:	Concurrently Herewith
For	:	METHOD OF ENHANCING DELIVERY OF A THERAPEUTIC NUCLEIC ACID

New York, New York
July 11, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

PRELIMINARY AMENDMENT

Sir:

Prior to examining the above-identified application, kindly amend the application as follows:

IN THE SPECIFICATION

Please replace the paragraph on lines 3-6 on page 1 with the following paragraph:*

This application is a continuation of PCT International application number PCT/US02/01797, filed January 22, 2002, which claims benefit of United States

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*Applicants attach Appendix A, which shows where changes in the specification have been made. Underlines indicate additions. Brackets indicate deletions.

provisional application number 60/263,416, filed January 22, 2001. The disclosures of International application PCT/US02/01797 and United States provisional application 60/263,416 are incorporated by reference herein.

IN THE CLAIMS

Please cancel claims 2-33.

Please amend claim 1 as follows:*

1. (Amended) A method for increasing the level of a therapeutic gene product in a subject, the method comprising administering to said subject a first viral vector which comprises a therapeutic nucleic acid encoding said therapeutic gene product and an agent that modulates Kupffer cell function in said subject, wherein said agent is a second viral vector that does not comprise said therapeutic nucleic acid.

Please add claims 34-53 as follows:

34. (Added) A method for increasing the level of a therapeutic gene product in a subject, the method comprising administering to said subject a viral vector comprising a therapeutic nucleic acid encoding said therapeutic gene product and an agent that modulates Kupffer cell function in said subject, wherein said agent

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*Applicants attach Appendix B, which shows where changes in the claims have been made. Underlines indicate additions. Brackets indicate deletions.

is administered less than 1 hour prior to administering said viral vector.

35. (Added) The method according to claim 34, wherein said agent is administered less than five minutes prior to administering said viral vector.

36. (Added) A method for increasing the level of a therapeutic gene product in a subject, the method comprising administering to said subject a viral vector comprising a therapeutic nucleic acid encoding said therapeutic gene product and an agent that modulates Kupffer cell function in said subject, wherein said agent is administered concurrently with the viral vector.

37. (Added) A method for increasing the level of a therapeutic gene product in a subject, the method comprising administering to said subject a viral vector comprising a therapeutic nucleic acid encoding said therapeutic gene product and an agent that modulates Kupffer cell function in said subject, wherein said agent is a particle sufficient for phagocytosis and has a diameter of about 10 nm to about 1000 nm.

38. (Added) The method according to claim 1, wherein said first and/or second viral vector is an adenovirus vector.

39. (Added) The method according to any one of claims 34-38, wherein said viral vector is an adenovirus vector.

40. (Added) The method according to claim 1, wherein said subject is a rodent.

41. (Added) The method according to any one of claims 1 or 34-38, wherein said subject is a primate.

42. (Added) The method according to claim 41, wherein said primate is a human.

43. (Added) The method according to claim 1, wherein said first viral vector is administered by a route selected from the group consisting of oral administration, nasal administration, parenteral administration, transdermal administration, topical administration, intraocular administration, intrabronchial administration, intraperitoneal administration, direct injection into cells, tissue, organ or tumor, intravenous administration, subcutaneous administration, and intramuscular delivery.

44. (Added) The method according to any one of claims 34-37, wherein said viral vector is administered by a route selected from the group consisting of oral administration, nasal administration, parenteral administration, transdermal administration, topical administration, intraocular administration, intrabronchial administration, intraperitoneal administration, direct injection into cells, tissue, organ or tumor, intravenous administration, subcutaneous administration, and intramuscular delivery.

45. (Added) The method according to any one of claims 1, 34-37, wherein said agent is administered by a route selected from the group consisting of oral administration, nasal administration, parenteral administration, transdermal administration, topical administration, intraocular administration, intrabronchial, intraperitoneal administration, direct injection into cells, tissue, organ or tumor, intravenous administration, subcutaneous administration, and intramuscular delivery.

46. (Added) The method according to any one of claims 34-37, wherein said viral vector is a replication-defective viral vector.

47. (Added) A method of modulating toxicity associated with a virally encoded transgene, the method comprising administering to a subject an agent that modulates Kupffer cell level or Kupffer cell function in said subject.

48. (Added) The method according to claim 47, wherein said agent is administered prior to administration of a therapeutic nucleic acid encoding a therapeutic gene product.

49. (Added) The method according to claim 47, wherein said toxicity is hepatotoxicity.

50. (Added) A method for modulating delivery of a virally encoded transgene to a subject, the method

comprising:

(a) identifying a dosage inflection point of a virus containing said virally encoded transgene in said subject;

(b) comparing said inflection point to levels of a product of said virally encoded transgene in said subject; and

(c) adjusting if necessary the dose of virus administered to said subject, thereby modulating dosage of said virally encoded transgene.

51. (Added) A method for modulating delivery of a virally encoded transgene to a subject, the method comprising:

(a) identifying a first dosage inflection point of a first virus not containing said encoded transgene in said subject, thereby saturating a Kupffer cell function;

(b) identifying a second dosage inflection point of a second virus containing said virally encoded transgene in said subject, wherein the dosage curve is non-linear;

(c) comparing said second inflection point to levels of a product of said virally encoded transgene in said subject; and

(d) adjusting if necessary the doses of the first virus and second virus administered to said

subject, thereby modulating dosage of said virally encoded transgene.

52. (Added) A pharmaceutical composition comprising a viral nucleic acid encoding a therapeutic gene product, an agent that modulates Kupffer cell function, and a pharmaceutically acceptable carrier.

53. (Added) The pharmaceutical composition according to claim 52, wherein said viral nucleic acid is provided in a viral particle.

54. (Added) The method according to claim 1, wherein said first and/or second viral vector is a replication-defective viral vector.

REMARKS

Applicants have updated the related application information by amendment of the first paragraph beneath the Title on page 1. Applicants have canceled claims 2-33 without prejudice and without waiver of their right to pursue any canceled subject matter in a divisional or continuing applications claiming priority from this application or a related application.

Applicants have amended claim 1. Support for amended claim 1 is found, e.g., in original claims 1 and 8. Applicants have added claims 34-53. Support for claims 34-35 is found, e.g., in original claims 1, 10 and 12-13. Support for claim 36 is found, e.g., in original

claims 1 and 14. Support for claim 37 is found, e.g., in original claims 1 and 15-16. Support for claim 38-39 is found, e.g., in the Specification at page 12, line 4-5 and page 11, lines 13-16 and original claims 1, 2 and 9. the Specification at page 12, line 4-5 and page 11, lines 13-16 and original claims 1, 2 and 9. Support for claim 40 is found, e.g., in original claims 1 and 17. Support for claim 41-42 is found, e.g., in original claims 1, 18-19 and the Specification at page 16, lines 18-23. Support for claim 43-45 is found, e.g., in original claims 1, and 20-22. Support for claim 46 and 54 are found, e.g., in original claims 1, 8 and 24 and original claim 23 and the Specification at page 11, line 16-17. Support for claim 47-49 is found, e.g., in original claims 27-29. Support for claim 50 is found, e.g., in original claim 30. Support for claim 51 is found, e.g., in original claim 31. Support for claim 52 is found, e.g., in original claim 32. Support for claim 53 is found, e.g., in original claims 1 and 33.

None of the above-listed amendments to the claims goes beyond the disclosure in the application as filed.

CONCLUSION

Applicants request early allowance of the pending claims.

Respectfully submitted,

James F. Haley, Jr. (Reg. No. 27,794)
Stanley D. Liang (Reg. No. 43,753)
Attorneys for Applicants
Kyumin K. Lee (Reg. No. 53,195)
Agent for Applicants
c/o FISH & NEAVE
1251 Avenue of the Americas
New York, New York 10020
Tel.: (212) 596-9000
Fax: (212) 596-9090